New Therapies and Technologies in Diabetes 2006

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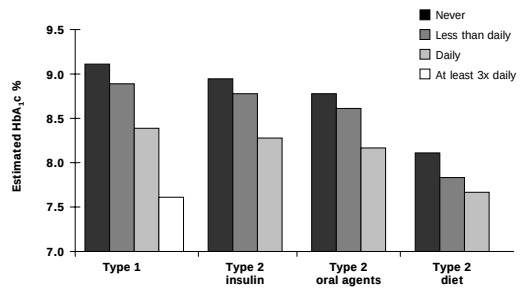
THE UNIVERSITY OF UTAH

Continuous Glucose Monitoring: Why All the Fuss?

Relationship Between SMBG and HbA_1c in a Large Cohort from a Managed Care Organization



Karter, et al. *Am J Med* 2001;111:1-9.

Statistically-Fitted Curve for A_1c as a Function of the SMBG Tests Per Day

(Data from 378 adults with type 1 diabetes on pump therapy)

Investigators found a regression equation could be derived predicting HbA_1c:

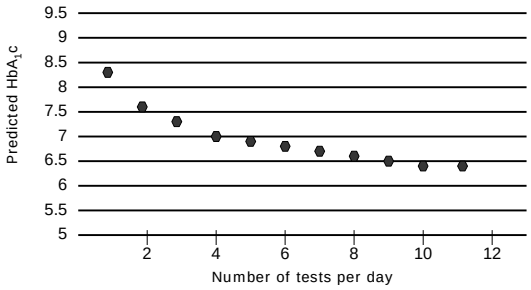
$HbA_1c = 5.99 + 5.32/([\text{number of glucose tests per day}] + 1.39)$

The fitted curve provides persuasive evidence as to the importance of frequent BG testing

Davidson PC, et al. Abstracts from the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 430-P

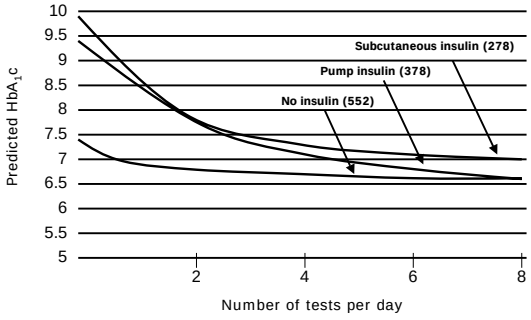
Statistically-Fitted Curve for A_1c as a Function of the SMBG Tests Per Day

(Insulin Pump Therapy)



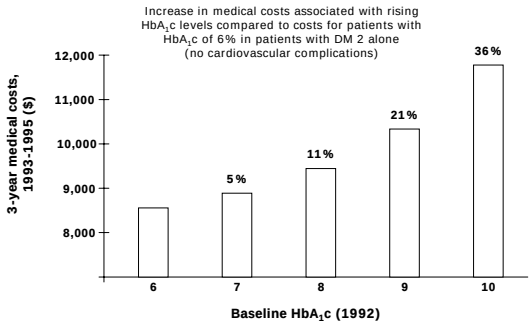
Davidson PC, et al. Abstracts from the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 430-P

Statistically-Fitted Curve for A_1c as a Function of the SMBG Tests Per Day



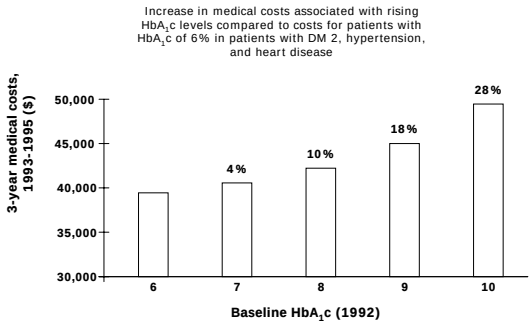
Davidson PC, et al. Abstracts from the 65th Scientific Sessions of the American Diabetes Association; June 10-14, 2005; San Diego, California. Abstract 408-P

Healthcare Costs Increase with Worsening Glycemic Control



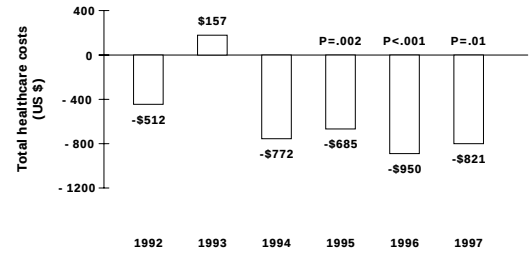
Gilmer TP, et al. *Diabetes Care* 1997;20:1847-1853.

Healthcare Costs Increase with Worsening Glycemic Control



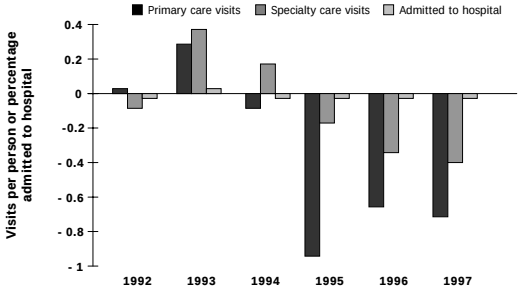
Gilmer TP, et al. *Diabetes Care* 1997;20:1847-1853.

Adjusted Mean Differences in Costs by Year Between Patients with Diabetes Whose HbA_1c Improved by ≥1% or Did Not Improve



Wagner EH, et al. *JAMA* 2001;285:182-189.

Adjusted Mean Differences in Utilization by Year Between Patients with Diabetes Whose HbA_1c Improved by ≥1% or Did Not Improve



Wagner EH, et al. *JAMA* 2001;285:182-189. P <0.05 for all after 1992

Diabetic Vascular Complication Risk Reduction per 1% Decrease in HbA_1c

Study	Eye	Kidney	Nerve	Heart
DCCT	27-38%	22-28%	29-35%	40%*
Kumamoto	28%	50%	↑ NCV	25%*
UKPDS	19%	26%	18%	14%

* Not statistically significant because of a small number of events; all other values significant

NCV = nerve conduction velocity

Continuous Glucose Monitoring: The Technology

Interstitial Fluid (ISF) Measurement

- ISF (G2) is highly comparable to blood glucose (G1) because ISF is fed by the capillaries
- Steady-state difference between blood and ISF is compensated for by sensor calibration
- During rapid changes in blood glucose the 10 minute ISF response lag time is accounted for in the CGMS software algorithm

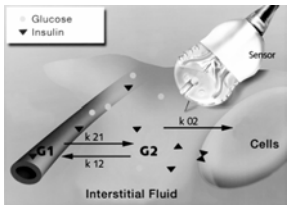


Illustration adapted from Rebrin K, et al., Amer Phys Soc 1999; E562.

Continuous Glucose Monitoring

(Data from 8 adults with type 1 diabetes and 16 adults with insulin-requiring type 2 diabetes who used a CGMS)

The 24 patients had an average of 13.8 ± 6.6 paired sensor/meter readings

15% Mean absolute difference (MAD) between fingerstick capillary glucose and sensor data

96% of patients had hyperglycemia and 63% of patients had hypoglycemia not detected by capillary glucose testing

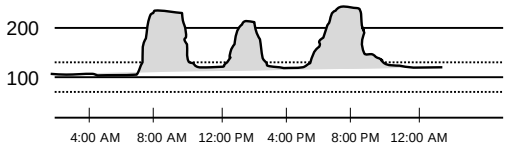
Lee SW, et al. Abstracts from the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 444-P

Continuous Glucose Monitoring

(Determinants of HbA_1c from data in 60 adults with type 1 diabetes)

Attempt to determine if, in patients with type 1 diabetes CGMS values are associated with HbA_1c independently of data provided by clinical evaluation, laboratory tests and SMPG

Variable	p
CGMS Postprandial Glycemia (mg/dl*min)	0.002



Gertzman J, et al. Abstracts from the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 436-P

Continuous Glucose Monitoring

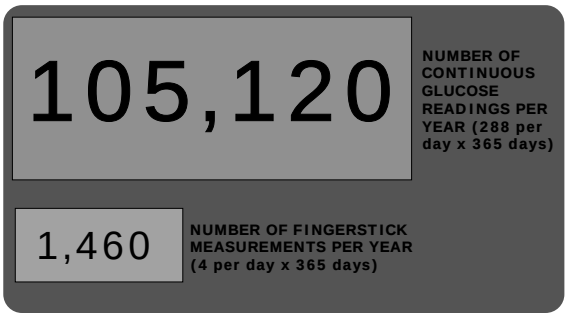
(Data from 378 adults with type 1 diabetes on pump therapy)

'Standard of care' in type 1 diabetes = 4 – 6 SMBG per day

4 – 6 minutes / 1440 minutes per day = 0.27 – 0.42% of the day

Blood glucose = 145 mg/dL → ↗ ↗ ↘

More Information With Continuous Glucose Monitoring



Real-Time Continuous Glucose Monitoring

Does it really work
(does having more info help)?

Are there drawbacks?

Guardian® RT*

System Description

- A glucose sensor is inserted in subcutaneous tissue, usually in the abdominal area using an insertion device (SenSerter®)
- The patient wears the same sensor for up to 3 days during normal daily activities (288 glucose readings per day)
- The wireless monitor is worn discreetly like a pager on a belt or in a pocket and updates its real-time glucose display every 5 minutes
- It also provides high and low glucose alarms
- BG from only two fingersticks per day are used to calibrate the monitor
- Data collected in Guardian RT can be downloaded to a computer for further analysis

Continuous Glucose Monitoring

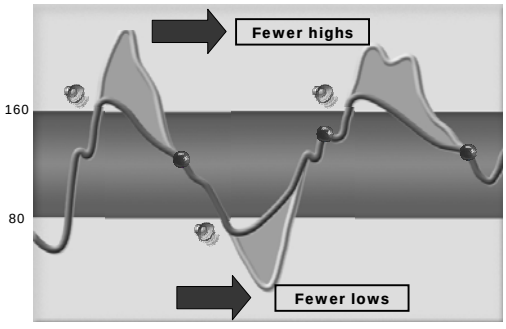
(GuardControl Study - European multicenter trial of 162 patients with type 1 diabetes wearing Medtronic Guardian RT system)

The group that wore the continuous monitor throughout the trial achieved a substantial decrease in A_1C of 1.1 points compared with a 0.4-point reduction for the placebo group. A third group that wore the device intermittently saw a decline in A_1C of 0.7 points.

Further, patients in the continuous-monitoring group had meaningful decreases in excursions in glucose below 70 and over 190, yielding significantly less glycemic instability and fewer "swings."

EASD 2005: Abstract 124. Presented Sept. 13, 2005

More Information With Continuous Glucose Monitoring



Continuous Glucose Monitoring

(GuardControl Study - European multicenter, randomized controlled trial of 162 patients with type 1 diabetes)

Potential Benefits Based on GuardControl Study

Improved, independent, pro-active blood glucose management

Reduced number of trips to ER for both severe hypoglycemia and severe hyperglycemia & DKA

Impact on cost of long-term complications of diabetes

EASD 2005: Abstract 124. Presented Sept. 13, 2005

Continuous Glucose Monitoring

(71 Adults with type 1 diabetes using the Medtronic Guardian RT system)

Patients randomized to hyper- or hypoglycemia alerts

Monitor readings on average 13 mg/dL lower than paired meter readings

The hypoglycemia alert distinguished glucose values $\leq$ 70 mg/dl with 67% sensitivity and 90% specificity

The hyperglycemia alert detected glucose values $\geq$ 250 mg/dl with 63% sensitivity and 97% specificity

Mastrototaro, et al. Abstracts from the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 12-OR

A Randomized Controlled Study of a Transcutaneous, Real-Time Continuous Glucose Sensor Demonstrates Improvement in Glycemic Control

(91 patients with type 1 or 2 diabetes using the DexCom Inc. system)

Control group = blinded to sensor data all 3 72-hour periods

'Display' group = blinded during first 3 days and unblinded during second and third 3-day periods to sensor glucose data

'Display' group spent 21% less time low (<55 mg/dl), 23% less time high (>240 mg/dl) and 26% more time in the target glucose range (81-140 mg/dl) versus control group ($p<0.0001$)

Within the 'Display' group patients improved glycemic control within 6 days!

Jovanovic L, et al. *Diabetes Care* 2006;29:44-50.

A Randomized Controlled Study of a Transcutaneous, Real-Time Continuous Glucose Sensor Demonstrates Improvement in Glycemic Control
(91 patients with type 1 or 2 diabetes using the DexCom Inc. system)

Period 1 (blinded) median glucose = 200 mg/dl

Period 2 (unblinded) median glucose levels = 178 mg/dl

Period 3 (unblinded) median glucose levels = 148 mg/dl

Jovanovic L, et al. *Diabetes Care* 2006;29:44-50.

Results from a Real-Time Unblinded Study of a Short-Term Continuous Glucose Sensor in Subjects with Type 1 Diabetes
(15 patients with type 1 diabetes using the DexCom Inc. system)

Treatment group = patients wore sensor for two 72-hour periods and glucose checked every 20 minutes for first 12 hours and subsequently 7 per day at home

Mean Absolute Relative Difference (MARD) was 21% between blood and sensor glucose values

Sensitivity and specificity of high and low glucose alerts at thresholds of 200 and 80 mg/dl were:

85% sensitivity and 89% specificity $\geq$200 mg/dl

84% sensitivity and 83% specificity $\leq$ 80 mg/dl

Real-Time Continuous Glucose Monitoring May be Best Used for 'Trend Analysis'

Continuous Glucose Monitoring

(Continuous Glucose Sensors Seen Best for Glucose Trend Analysis – 13 patients with type 1 diabetes during rapid glucose excursions)

Medtronic needle-type CGMSgold sensor vs. Menarini Diagnostics microdialysis-based GlucoDay sensor

GlucoDay significantly more accurate than CGMSgold sensor

Mean absolute differences (MADs) between sensor and blood glucose values significant (15.0% for CGMSgold and 13.6% for GlucoDay sensor)

Accuracy clearly deteriorated in the hypoglycemic range, especially for the CGMSgold with MAD of 24%

Diabetes Care 2005;28:2871-2876.

Continuous Glucose Monitoring

13-20% mean absolute differences and ≈ 10 minute delay from blood glucose values make trend analyses most valuable

Individual sensor readings should probably be used with caution

Continuous Glucose Monitoring

Advantages

Improved overall glucose control

- Earlier detection of hyperglycemia (upper limit alarm)
- Earlier detection of hypoglycemia (lower limit alarm)

Improved ability to exercise/drive safely

Improved sense of well-being – "I'm in control of my diabetes"

No evidence for more frequent hypoglycemia - 'over-correcting'

Continuous Glucose Monitoring

Disadvantages

Lag in sensor data during rapid glucose excursions

'Bulky' medical device on abdomen/hip (exercise, sleep, etc)

Inability to disconnect from device? (wireless technology)

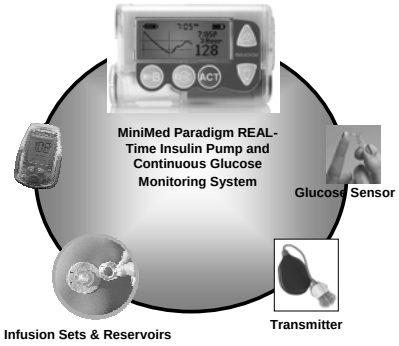
Time required to replace sensor/re-connect to monitor

Over-reacting to continuous glucose data (stacking boluses)

Cost of system ($2700) and sensors ($300 per month)

Sensor-Augmented Insulin Pump

(Medtronic MiniMed 522 and 722 System – April 2006)



Newer Therapies in Diabetes 2006

(Insulin Pump Therapy - CSII)

- Inappropriate Patient Selection:

Patients with unreasonable expectations of insulin pump therapy

Patients who do not have well-established carbohydrate and insulin sensitivity factors

Patients non-compliant with FSBG measurements and other requests (dietary logs, carbohydrate counting, etc.)

Patients with poor vision or manual dexterity

Newer Therapies in Diabetes 2006

(Endocannabinoid Receptor Antagonists)

- Rimonabant – an endocannabinoid receptor antagonist:

Rimonabant In Obesity-Diabetes (RIO-Diabetes)

RIO-Diabetes was a multicenter, randomized, double-blind, placebo-controlled study of 1,045 diabetic patients. The mean BMI of patients was 34 and their mean waist circumference was 43.3 inches. Patients had a mean HbA1c of 7.5%. 1 year follow up.

Among patients treated with Rimonabant, 68% lowered A_1c below 7%

Over one year patients lost 11.7 lbs and 2.05 inches in waist circumference

HDL increased by 6.6 mg/dL, and triglycerides lowered by 31.6 mg/dL

Scheen A. Late breaking clinical trials. *65th Scientific Sessions of the ADA*; June 10-14, 2005; San Diego, CA.

Newer Therapies in Diabetes 2006

(Endocannabinoid Receptor Antagonists)

		Rimonabant	
	PLACEBO (n)	5 mg (n)	20 mg(n)
	Baseline	Baseline	Baseline
IFG	100% (290)	100% (492)	100% (508)
	1 Year	1 Year	1 Year
NFG	39.2% (105)	41.5% (186)	46.5% (218)
IFG	56.0% (150)	54.5% (244)	49.9% (234)
T2DM	4.9% (13)	4.0% (18)	3.6% (17)

IFG: Impaired Fasting Glucose; NFG: Normal Fasting Glucose; T2DM: Type 2 Diabetes

Rosenstock. *65th Scientific Sessions of the ADA*; June 10-14, 2005; San Diego, CA. Abstract 13-LB

Newer Therapies in Diabetes 2006

(Glucagon-like peptide (GLP)-1 analogs)

GLP-1 released from L-cells in intestinal mucosa in response to carbohydrate or fat intake

Peptide with half-life of 2 minutes

Enhances insulin secretion while suppressing inappropriately high glucagon secretion in the presence of elevated glucose levels

Helps match glucose appearance to glucose disappearance by slowing gastric emptying

Regulates food intake in the hypothalamus?

Newer Therapies in Diabetes 2006
(Glucagon-like peptide (GLP)-1 analogs)

- Exenatide – a (GLP)-1 analog:

An open-label extension (82-104 weeks) trial in obese patients with type 2 diabetes

Exenatide therapy resulted in significant reductions both triglycerides and diastolic blood pressure

Average A_1c reduction of 1.2% and continued weight loss averaging > 4 kg after the 82 weeks of treatment

Kendall DM, et al. *65th Scientific Sessions of the ADA*;June 10-14, 2005; San Diego, CA. Abstract 16-OR

Newer Therapies in Diabetes 2006
(DPP-IV Inhibitors)

Enzymes that rapidly break down GLP-1 and other peptides

DPP-IV 'knockout' mice are resistant t diet-induced obesity, insulin resistance, and type 2 diabetes

Reduce glucose levels (especially postprandial levels) without changing insulin levels

Animal studies demonstrate increase in β-cell mass

Newer Therapies in Diabetes 2006
(DPP-IV Inhibitors)

- Vildagliptin – a DPP-IV inhibitor:

Typically dosed at 50-100 mg/day single or divided doses

Hemoglobin A_1c levels typically improved by ≈ 0.5 - 1%

Fasting and mean plasma glucose levels improved by about 20 and 40 mg/dl respectively

Weight loss of 0.5 kg in 1-year trial

J Clin Endocrinol Metab 2004;89(5):2078-2084.
Diabetes 2004;53(suppl 2):A8.
Diabetes Care 2004;27(12):2874-2880.

Newer Therapies in Diabetes 2006
(DPP-IV Inhibitors)

- Sitagliptin – a DPP-IV inhibitor:

Oral glucose tolerance testing performed 2 hours after dosing sitagliptin in 56 patients with type 2 diabetes

Increased GLP-1 levels 2-fold

Increased plasma insulin AUC significantly

Increased C-peptide AUC significantly

AUC for glucagon decreased significantly

Decreased glucose AUC by ≈ 25%

Diabetes 2004;53(suppl 2):A82.

Newer Therapies in Diabetes 2006
(DPP-IV Inhibitors - Summary)

Several in clinical development

Minimal gastrointestinal adverse effects

Concerns regarding adverse immunologic effects

Weight neutral

Well-tolerated in early-phase studies
(pruritis, GI upset, dizziness, hypoglycemia, and diaphoresis)

Advantage due to oral delivery?

Newer Therapies in Diabetes 2006
(Incretin mimetics and DPP-IV Inhibitors - Summary)

Drug Class, Research Name	Generic Name	Manufacturer	Status
DPP-IV inhibitors			
LAF237	Vildagliptin	Novartis Pharmaceuticals	Phase III
MK-0431	Sitagliptin	Merck and Co., Inc.	Phase II-III
Incretin Mimetics			
AC2993 (exendin-4)	Exenatide	Amylin Pharmaceuticals, Inc. and Eli Lilly and Co.	Phase III
NN2211	Liraglutide	Novo Nordisk A/S	Phase IIb
CJC-1131	Not determined	ConjuChem	Phase II
ZP10	Not determined	Sanofi-Aventis	Phase II
Albugon	Not determined	Human Genome Sciences	Phase II

Newer Therapies in Diabetes 2006
(Inhaled Insulin - Background)

Exubera is the first noninjectable insulin with efficacy comparable to that of regular insulin

It can be used as an alternative to rapid-acting insulin in combination with longer-acting insulin in patients with type 1 diabetes mellitus, and alone or in combination with longer-acting insulin and/or oral agents in patients with type 2 diabetes

Exubera appears to be safe for use in nonsmoking patients with normal lung function

As part of the drug approval process, Pfizer is required to study pulmonary function in 5000 patients over a period of 5 years

1. *Exubera* Package Insert. New York, NY: Pfizer; January 2006.
2. Barclay L. *Exubera* approved despite initial lung function concerns. Available at: http://www.medscape.com/viewarticle/523294?rss. Medscape Medical News. Posted 02/09/2006. Accessed May 1, 2006.
3. *Exubera* Update: Lungs, bioavailability and hypoglycemia. Available at: http://www.diabetesincontrol.com/modules.php?name=News&file=article&sid=3481. Accessed May 1, 2006.

Newer Therapies in Diabetes 2006
(Inhaled Insulin - Data)

Intermediate onset and duration of action between rapid-acting analogs and regular insulin

Similar HbA_1c reductions compared to regular insulin

Less hypoglycemia with Exubera versus regular insulin

Significant more cough (≈30%) with Exubera versus subcutaneous insulin, typically within minutes of inhalation and usually mild

Norwood, P et al. Program and abstracts of the European Association for the Study of Diabetes 41st Annual Meeting; September 12-15, 2005; Athens, Greece. Abstract 73.

Newer Therapies in Diabetes 2006
(Issues with Inhaled Insulin)

Most patients will still require a longer-acting insulin

Exubera is inhaled through a device about the size of a flashlight - ambulatory patients may have to carry this device with them

Exubera will cost about $4 a day in the United States

Exubera is costly, short-acting, and delivered in a bulky container - once these limitations are overcome, we may see a drug that will substantially replace injectable insulin

1. *Exubera* Package Insert. New York, NY: Pfizer; January 2006.
2. Barclay L. *Exubera* approved despite initial lung function concerns. Available at: http://www.medscape.com/viewarticle/523294?rss. Medscape Medical News. Posted 02/09/2006. Accessed May 1, 2006.
3. *Exubera* Update: Lungs, bioavailability and hypoglycemia. Available at: http://www.diabetesincontrol.com/modules.php?name=News&file=article&sid=3481. Accessed May 1, 2006.

Newer Therapies in Diabetes 2006
(Insulin)

Other 'alternative' insulin formulations:

- Oral insulins:
  - *Oralin*, an oral insulin spray produced by Generex Biotechnology Corporation
  - An oral insulin produced by Emisphere Technologies
  - *Insulin 105*, an orally delivered insulin produced by NOBEX Corporation
- Inhaled insulins:
  - *AERx* Diabetes Management System produced by Novo Nordisk
  - *Technosphere* insulin by MannKind Corp.
  - Human insulin inhalation powders by Lilly/Alkermes and by Kos Pharmaceuticals

Newer Therapies in Diabetes 2006
(Pathophysiologic Effects of Drugs for the treatment of Type 2 DM)

Drug Class	Insulin Deficiency	Insulin Resistance	Excessive Hepatic Glucose Production	Inappropriate Elevated Glucagon Secretion	Gastric Emptying Dysregulation	Body Weight Dysregulation
Biguanides	None	Beneficial	Beneficial	None	None	Neutral
TZDs	None	Beneficial	Beneficial	None	None	Increase
α-glucosidase inhibitors	None	None	None	None	None	Neutral
Sulfonylureas	Beneficial	None	None	None	None	Increase
Meglitinides	Beneficial	None	None	None	None	Neutral
Insulin	Beneficial	None	None	None	None	Increase
Amylinomimetics	None	None	None	Beneficial	Beneficial	Decrease
Incretin mimetics	Beneficial	None	None	Beneficial	Beneficial	Decrease
DPP-IV inhibitors	Beneficial	None	None	Beneficial	Unknown	Neutral